Estimation of the Severity of Aortic Valve Stenosis by Frequency Analysis of the Murmur

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This study of 23 patients was designed to test the hypothesis that the severity of aortic stenosis can be estimated by application of the principle that higher murmur frequencies are generated as severity of the stenosis increases. The frequency content of the systolic murmur of aortic stenosis was determined using fast Fourier transform spectral analysis and correlated blindly with the transvalvular peak systolic pressure gradient. The 23 patients averaged 52 years of age (range 29 to 70). The systolic pressure gradient ranged between 10 and 140 mm Hg. After cardiac catheterization, the electrocardiogram and sound vibrations from the aortic area and cardiac apex were recorded on tape. The R wave initiated analog to digital conversion for the duration of the murmur. Frequency spectra of 10 murmurs were computed to obtain an average spectrum, which was normalized to minimize coupling and transmission variability.

The plot of murmur frequency versus magnitude from 25 to 75 Hz (constant area) and that from 75 to 150 Hz (predictive area) were computer-integrated. The integrated areas were normalized for comparison of patients by calculating the ratio of predictive area to constant area. This ratio recorded at the aortic area increased linearly as systolic pressure gradient increased ($r = 0.90$, $p < 0.001$); at the cardiac apex this ratio did not correlate with the systolic pressure gradient. The predictive/constant area ratio at the aortic area correlated less well with calculated valve area and the degree of calcification, and was independent of the degree of regurgitation. The severity of aortic stenosis may be underestimated by the predictive/constant area ratio in patients with a low cardiac output, in whom the systolic pressure gradient would also be reduced. Nevertheless, this noninvasive technique may prove useful in predicting the need for cardiac catheterization and in longitudinal follow-up of a majority of patients with aortic stenosis.

The hallmark of aortic valve stenosis is a systolic ejection murmur. However, a systolic ejection murmur is common in older persons and may signify nothing more than hemodynamically insignificant thickening and calcification of the valve cusps or roughening of the aortic root. In the symptomatic patient, the murmur is more likely to alert the examiner to further investigation, including cardiac catheterization. In the older adult, the symptoms associated with severe aortic stenosis (exertional dyspnea, angina pectoris and syncope) may, in fact, result from associated pulmonary, coronary artery or cerebral vascular disease, and at cardiac catheterization, an insignificant aortic valve gradient may be found.

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The literature is replete with conflicting results regarding the efficacy of certain physical findings and noninvasive tests in the diagnosis of severe aortic stenosis. In general, abnormal physical findings and noninvasive tests, either singly or in combination, are highly predictive of severe stenosis when they are present, but in the majority of patients with severe stenosis, the findings are not diagnostic. The usual criteria of severe aortic stenosis are particularly unreliable in the elderly (1–3).

There is a need for a noninvasive test that more accurately predicts the severity of aortic stenosis and can screen patients for cardiac catheterization. This study was designed to test the hypothesis that the severity of aortic stenosis can be estimated by application of a basic hydrodynamic principle which predicts that higher murmur frequencies are generated as the severity of the stenosis increases.

The hemodynamics of aortic stenosis are comparable in many respects with the hydrodynamics associated with a localized narrowing in a tube. The Strouhal relation was developed to predict the frequency of the fluid vibrations

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produced by flow in such a hydrodynamic system. This relation, developed for steady-state Newtonian flow, is as follows: f = KU/D (where f = frequency produced, K = a system-dependent constant, U = velocity of flow and D = orifice diameter). This equation shows that as orifice diameter decreases or velocity increases, the frequency of the vibrations produced should also increase. Applicability of this relation has been verified in the human cardiovascular system by Lees et al. (4–6). These workers have demonstrated that the estimated luminal diameter (D) of a carotid arterial stenosis was predicted by the rearranged Strouhal formula: $D = U/F_0$, where U = an assumed velocity of 500 cm/s and F_0 = "break frequency." Flow through a stenotic aortic valve should follow the same hydrodynamic principle, which was verified in discrete carotid stenosis.

However, many dissimilarities exist between carotid stenosis and aortic stenosis. From a hydrodynamic standpoint, the carotid system approximates a straight tube with a centrally located circular orifice. In aortic valve stenosis, poststenotic diameters may vary considerably, the aortic arch is curvilinear and the valvular orifice is frequently not circular. In addition, there are a number of variables that probably affect the intrinsic frequency of the murmur. Aortic stenosis is a complex pathologic entity with variability in the degree of calcification, the number of cusps, the presence or absence of commissural fusion, the extent of poststenotic dilation and left ventricular function. Another major difference lies in the tissue interposed between these vibration sources and the area of sound recording. In valvular stenosis, two additional structures, namely, the bony thorax and lung parenchyma, are interposed. Although the general principles of hydrodynamics do not change, the system has changed, and therefore the algorithm that predicts the system should also change.

Another important theoretical consideration pertinent to this research is that as the severity of stenosis increases, the amount of energy converted to turbulence and wall vibrations should also increase. This principle was confirmed in human patients in a study (7) that measured turbulence in the ascending aorta. It was demonstrated that a low turbulent energy density was measured in patients with a normal aortic valve and normal flow and a higher turbulent energy density with a normal valve and high flow. The highest turbulent energy density was measured in those patients with a stenotic valve and high flow. Because of these general principles, vibration frequencies and their magnitudes should increase as the degree of stenosis and flow velocity increase. An investigation of the frequency spectra of sound vibrations in patients with aortic stenosis was undertaken to determine whether a significant relation with the invasively measured variables of severity could be derived.

Methods

Patient selection. Twenty-three consecutive and consenting adult patients referred with the diagnosis of aortic valve stenosis were studied (Table 1). Their average age was 52.4 years (range 29 to 70). These patients underwent phonocardiography soon after cardiac catheterization. The mean time interval between cardiac catheterization and phonocardiography was 3 days; 40% of the recordings were completed within 1 day and the remaining recordings within 2 weeks.

Invasive data acquisition. Indexes of severity were obtained at image intensification cardiac fluoroscopy and cardiac catheterization and included: 1) peak systolic pressure difference determined by pull-back of the catheter from the left ventricle into the aorta; 2) aortic valve orifice area calculated by the Gorlin formula (8) in those patients in whom it could be reliably calculated, that is, simultaneous flow and pressure measurements and less than 3+ aortic regurgitation; and 3) the degree of valvular calcification estimated fluoroscopically on a scale of 0 to 4 by a single experienced cardiovascular radiologist. In addition, the degree of aortic regurgitation, if present on aortography, was graded on a scale of 0 to 4 by the same radiologist using standard radiologic criteria (9); significant coronary artery disease was determined by the number of vessels with diameter narrowing of 70% or greater (Table 1).

Vibration analysis. After cardiac catheterization, the patients were taken to a soundproof room and a modified phonocardiogram was recorded. The murmur vibrations were sensed by a Hewlett-Packard 21050A contact microphone. The frequency response of the microphone was flat from 0.1 to 1700 Hz. To ensure consistent chest wall coupling, one investigator strapped the contact microphone to the chest in all patients. The microphone was placed normal to the plane of the chest wall and held with light pressure, enough to indent the skin by approximately 1 mm. A simultaneous electrocardiogram was also recorded on a dual channel magnetic tape recorder (Crown International, Inc.) (Fig. 1). The frequency response of the entire recording system was flat from 25 to 700 Hz. The signal from the chest wall vibrations was filtered with a 25 Hz high pass filter and a 1.5 kHz anti-aliasing filter (Krohn-Hite Corporation) to eliminate any frequency below the recording capabilities and above the frequency resolution capabilities of the data processing routines. The 1.5 kHz cutoff was chosen because frequencies above this limit would be unlikely to contribute significantly to the analysis. The recording was done in the supine position and at least 25 consecutive beats were recorded at the second right intercostal space and at the cardiac apex.

The data were analyzed on a Mod-Comp computer at the University of Cincinnati Computer Center. A standard delay of 90 ms after the peak of the QRS complex was chosen to eliminate all or most of the first heart sound without excluding any significant portion of the murmur vibrations. Ten consecutive murmur signals were analyzed to ensure a reproducible spectrum. Murmur sequences with extrasystolic, aberrantly conducted or post-extrasystolic beats were excluded. The murmur vibrations were then entered into the

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Table 1. Cardiac Catheterization Data

Case	Age (yr) & Sex	PA/CA	ΔPSP (mm Hg)	Valve Calcium (0 to 4)	AI (0 to 4)	Valve Orifice (cm^2)	CO (liters/min)	CI (liters/min per m^2)	Significant Coronary Artery Disease (no. of vessels)
1	40 M	0.333	10	1	0	1.8	6.7	3.9	0
2	56 M	0.244	12	2	2	—	5.6	2.5	0
3	29 M	0.259	16	3	3	—	—	—	0
4	56 M	0.320	56	1	0	0.70	5.74	2.4	0
5	65 F	0.361	37	3	0	—	—	—	2
6	40 M	0.416	50	2	3	—	4.92	2.8	1
7	32 M	0.425	85	0	3	—	5.7	3.0	0
8	70 M	0.833	140	4	4	—	4.89	2.5	1
9	50 M	0.528	60	3	2	0.84	5.8	3.2	0
10	47 M	0.300	30	4	1	1.12	7.36	3.7	0
11	52 F	0.540	102	3	1	0.49	6.04	3.4	0
12	64 F	0.629	103	4	0	0.74	5.8	3.3	1
13	53 M	0.563	116	4	0	0.44	5.18	2.5	0
14	45 M	0.554	83	3	3	—	6.44	3.4	1
15	67 F	0.549	50	1	1	0.79	5.70	2.8	3
16	37 F	0.523	60	2	0	1.1	6.97	4.2	—
17	65 M	0.487	58	0	0	0.70	6.72	3.1	0
18	55 M	0.367	47	3	1	0.63	3.89	2.0	2
19	53 F	0.766	137	4	0	0.37	4.41	2.8	0
20	64 M	0.335	42	2	3	—	—	—	1
21	53 M	0.296	40	2	2	—	4.33	—	0
22	56 M	0.256	20	1	3	—	5.02	2.54	0
23	58 F	0.532	75	3	0	0.765	8.06	3.48	1

AI = aortic insufficiency; CI = cardiac index; CO = cardiac output; PA/CA = predictive/control area ratio; ΔPSP = peak systolic pressure difference.

Mod-Comp computer through an analog to digital converter at a sampling frequency of 3,000 Hz to allow resolution of frequencies up to 1.5 kHz. The signal was then sampled for 341 ms so that all the murmur vibrations were included in the analysis. Each individual murmur then underwent a fast Fourier transformation. The transformations of all 10 murmurs were averaged to eliminate as much noise as possible and obtain an average spectrum that was free of beat to beat variation. The average spectrum was linearly plotted with the peak spectral value set to unity to normalize for coupling inconsistencies and variability in transthoracic transmission.

Statistical analysis. Data were analyzed by the Statistical Analysis System/Bio-Medical Data Package (SAS/BMDP), revision 79.5. Statistical analysis included general linear model, multiple regression analysis (BMDP9R-all possible subsets), as well as standard univariate, residual and plotting routines.

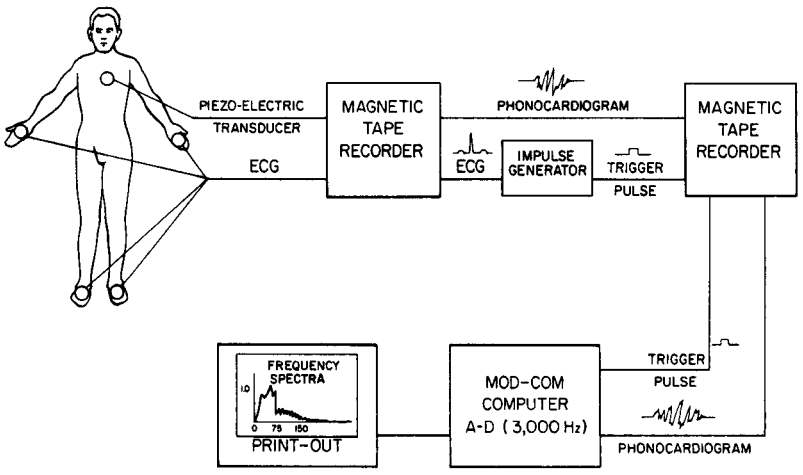

Figure 1. Diagram illustrating the recording system. See text for details. A-D = analog to digital; ECG = electrocardiogram.

Results

Murmur frequency plots. The frequency spectra of the murmurs of the 23 patients were examined for characteristic peaks, "break frequencies" or other features that could be correlated with severity. Examination of the frequency spectra plots revealed multiple peaks. However, a correlation between any major peak or peak pattern and the indexes of severity was not found. In general, frequency spectra showed a gradual decrease in amplitude as the frequency increased without an apparent break frequency. Careful visual examination of the spectral plots revealed a general trend between a greater energy content in the higher frequency range (predictive area = PA) and the degree of stenosis. However, there were individual exceptions to this correlation. In some patients, the peak systolic pressure difference was markedly increased, but the energy content in the higher frequency range was also diminished, suggesting the possibility of using the area in the low frequency range as a control area (CA), that is, to express predictive area (PA) relative to control area.

Algorithm for predicting severity of stenosis. The algorithm designed to quantify the observed differences was evaluated in this experiment as follows:

$$\text{PA/CA} = \int_{f_2}^{f_3} \text{A(f)df} / \int_{f_1}^{f_2} \text{A(f)df},$$

where A(f) = frequency amplitude, f_1 = starting frequency, f_2 = dividing frequency and f_3 = ending frequency. The starting frequency (f_1) was set at 25 Hz, which was dictated by the lower limit of the system frequency response. The dividing frequency (f_2) was varied from 60 to 90 Hz in 5 Hz increments and the ending frequency (f_3) was varied from 125 to 250 Hz in 5 Hz increments.

Because all 23 patients had a measured peak systolic pressure difference and only 13 had a calculated valve area, the peak pressure difference was chosen as the primary modeling variable. The best algorithm for prediction of severity was as follows:

$$\text{PA/CA} = \int_{75}^{150} \text{A(f)df} / \int_{25}^{75} \text{A(f)df}.$$

In other words, the optimized algorithm defined the predictive area (PA) as the energy content between 75 and 150 Hz and the control area (CA) as the energy content between 25 and 75 Hz. The term "predictive area" was selected because the energy content within this frequency range best predicted the severity of aortic stenosis.

Frequency plots versus systolic pressure gradients. The frequency plots and corresponding systolic pressure gradients in four patients are shown in Figure 2. In panel A, it is apparent that the area (energy) in the range between 75 and 150 Hz is smaller than the comparable predictive area in panels B, C and D which exhibit progressively larger areas that correspond to progressively larger valvular systolic gradients. Examples of individual exceptions in which the visual correlation between predictive area and severity was not obvious may be better appreciated by examination of the two frequency plots depicted in Figure 3. These two patients have similar areas in the higher frequency range (predictive area), but markedly different areas in the lower frequency range (control area). Panel A would correctly predict a more severe lesion if the predictive/control area ratio were used rather than predictive area alone.

Univariate and multivariate analyses (Table 2). All measured variables were normally distributed except for the valve area, which had 75% of its values between 0.5 and 1.1 cm^2 with 25% of the values spread between 1.2 and 1.9 cm^2. This distribution probably reflects a selection bias in referred cases. Multivariate analysis of the above variables revealed that the valve area (VA) was predicted best by the following model, where G = gradient and I = degree of insufficiency:

$$\text{VA} = 1.3 - 0.013\ \text{G} + 1.2\ \text{PA/CA} - 0.36\ \text{I}.$$

In this model, $r = 0.92$, $f = 17$ and $p < 0.001$. Not unexpectedly, the pressure gradient was the largest contributor to the correlation, while the predictive/control area (PA/CA) ratio contributed only slightly. In contrast, the best model for prediction of the pressure gradient was:

$$\text{G} = 127(\text{PA/CA}) - 21\ \text{I} - 51\ \text{VA} = 58.$$

In this model, $r = 0.96$, $f = 33$, $p < 0.0001$ and the single most significant predictor was predictive/control area (PA/CA) ratio. After removal of the invasive variables from the regression set, the best model was:

$$\text{G} = 128(\text{PA/CA}) + 7\text{C} - 12,$$

where C = degree of valvular calcification. This model was by far the best predictor of the pressure gradient using noninvasive indexes ($r = 0.93$, $f = 44$ and $p < 0.0001$). However, in this model, calcium contributed minimally to predictability. Therefore, a model utilizing only predictive/control area (PA/CA) ratio was evaluated to predict the pressure gradient. The relation is as shown in the following equation:

$$\text{G} = 214(\text{PA/CA}) - 34.$$

In this model, $r = 0.90$, $f = 96$ and $p < 0.0001$ (Fig. 4). The remaining variables were also independently correlated with the predictive/control area (PA/CA) ratio with the following correlation coefficients and probabilities: predictive/control area (PA/CA) ratio versus valve area, $r = 0.60$, $p < 0.06$ (Fig. 5); PA/CA ratio versus valvular calcification, $r = 0.41$, $p < 0.05$; and PA/CA versus degree of aortic insufficiency, $r = 0.02$, p = not significant.

Murmur vibrations in 19 patients were subdivided in time into thirds by a computer algorithm, such that the middle

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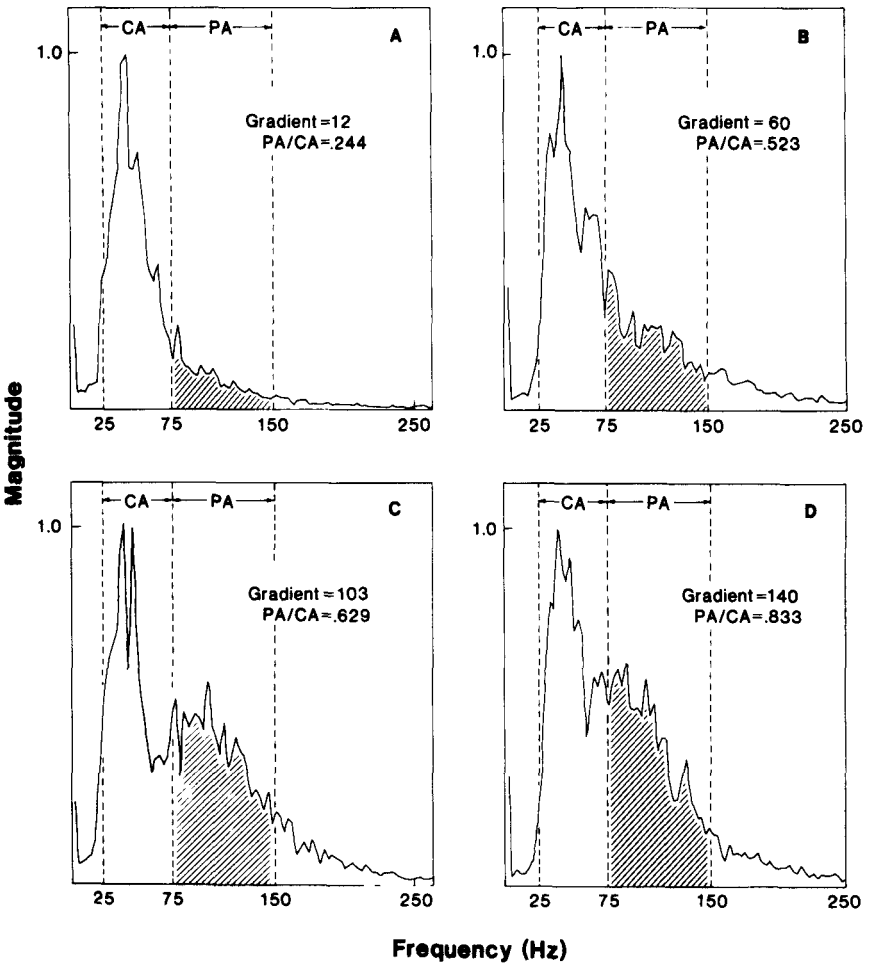

Figure 2. Frequency-magnitude plots of the murmur in four patients with aortic stenosis (**panels A to D**). The control areas (CA) from 25 to 75 Hz frequency are similar in all four patients. The predictive areas (PA) from 75 to 150 Hz clearly correlate with peak systolic pressure gradient, that is, predictive area (PA) progressively increases as the gradient increases between **A** and **D**.

third contained the peak of the murmur. Four patients were not analyzed for technical reasons. The highest correlation of predictive/control area ratio and valvular pressure gradient was found in the middle third of the murmur; this corresponded in time with the peak transvalvular pressure difference.

A very important aspect of these analyses was the finding that the predictive algorithm, which related predictive/control area (PA/CA) ratio to pressure gradient, was applicable to murmur vibrations recorded in the aortic area (second right intercostal space, parasternally), but not to murmurs recorded at the cardiac apex.

Discussion

This study demonstrates that a relation between higher frequencies and the degree of stenosis exists in patients with aortic stenosis. It confirms the hypothesis that the Strouhal concept is applicable to prediction of the severity of aortic stenosis in human beings. It is unlikely that the present algorithm would predict severity in all cases of aortic stenosis accurately; however, a high degree of correlation was demonstrated by this analysis.

Intensity versus frequency of the systolic murmur. Both the frequency content and the intensity of the systolic murmur of aortic stenosis are generated by disturbed flow and vortices and both are reduced by low flow. There are reasons to believe, however, that frequency analysis yields more specific information than would an analysis of intensity. The intensity of a murmur reflects only the most prominent portion of a frequency spectrum. Knowledge of the absolute intensity at each frequency could provide additional information, but this is currently unavailable with noninvasive techniques. To compare intensity with a standard would require recording sound at its source with a catheter tip transducer. A comparison of two of our patients with different body builds illustrates this point: a thin patient showed prominent frequency amplitudes at 75 Hz, whereas a heavy patient demonstrated prominent frequency amplitudes at 125 Hz. Although these two patients had markedly different frequency spectra and murmur configurations, the peak frequency amplitudes were almost identical. The thin patient was shown to have a small systolic pressure gradient. The heart vibrations produced in this patient were probably less intense than in the heavier patient who had a large systolic pressure gradient. In the thin patient, the vibrations were less attenuated and, therefore, the murmurs in the two patients were recorded as nearly identical in intensity.

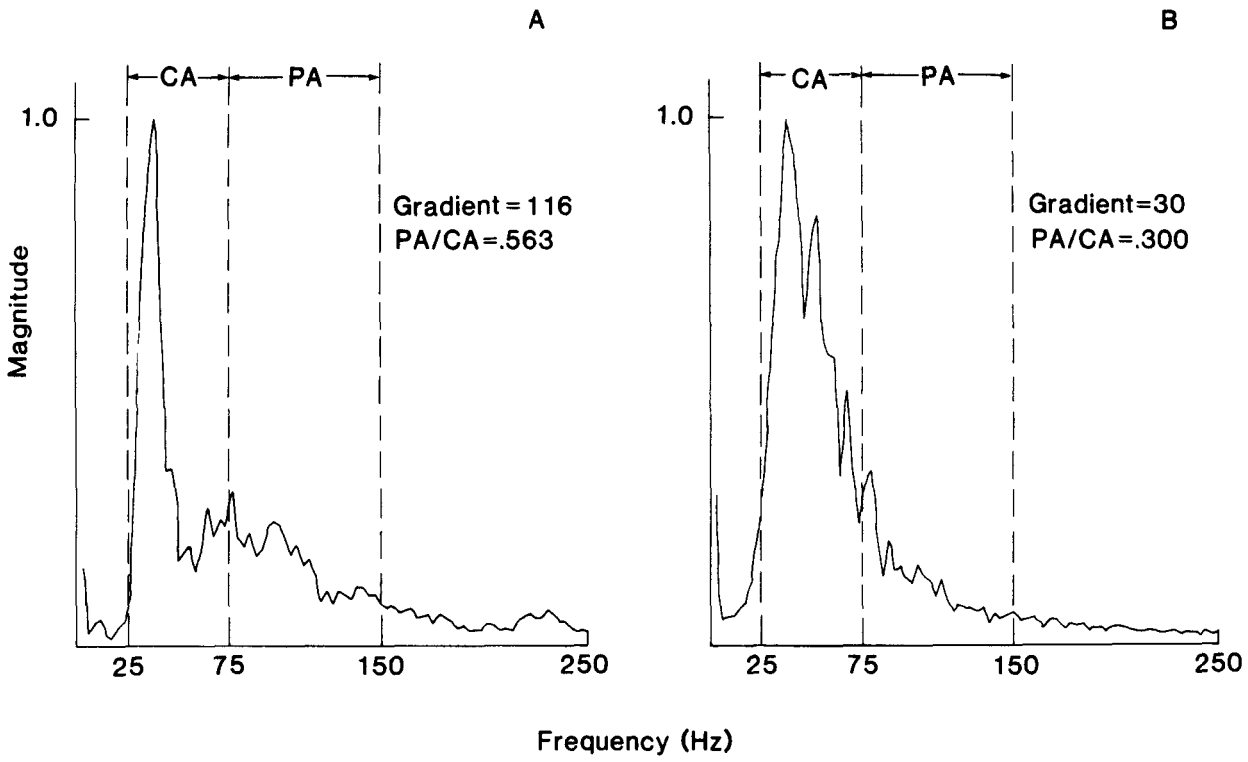

Figure 3. Frequency-magnitude plots in two patients with aortic stenosis are compared. The predictive area (PA) is similar in **panels A and B** although the peak systolic pressure gradient is clearly greater in **A**. When predictive area (PA) is normalized by dividing by the control area (CA), however, the predictive/control area (PA/CA) ratio is considerably greater in **A** and now correlates positively with the systolic pressure gradient.

Methodology. Several points of the analysis deserve further discussion. Predefined starting and stopping points for murmur analysis eliminated any bias that may have occurred due to operator intervention, and ensured inclusion of all the murmur vibrations of interest. This approach gave remarkably consistent results with predictive/control area (PA/CA) ratio, being reproducible within 1% on multiple analyses of different murmur sequences from the same patient. Although the aortic closure sound was included in some analyses, it contributed little to predictive/control area ratio because of its short duration relative to the murmur.

There is little doubt that patient selection has a major effect on any study of the sensitivity and specificity of a prognostic test in aortic stenosis. The patients in this study represent adults who were referred for cardiac catheterization by experienced cardiologists to evaluate the severity of their disease. Nine (39%) of the 23 patients had hemodynamically insignificant stenosis, defined as a pressure difference less than 50 mm Hg (Table 1). All patients with a predictive/control area ratio value above 0.4 would have been classified as having severe stenosis. Of the patients with a ratio below 0.4, it is notable that only one patient

Table 2. Univariate Statistics

Variable	Mean	Standard Deviation	Smallest Value	Largest Value
Ratio, PA/CA	0.453	0.160	0.244	0.833
Pressure gradient (mm Hg)	62	38	10	140
Valve area (cm^2)	0.76	0.40	0.24	1.80
Cardiac output (liters/min)	5.73	1.20	2.76	8.06
Degree of aortic insufficiency (0 to 4)	1.40	1.37	0	4
Degree of valvular calcification (0 to 4)	2.5	1.2	0	4
Age (yr)	52.4	11.3	29	70

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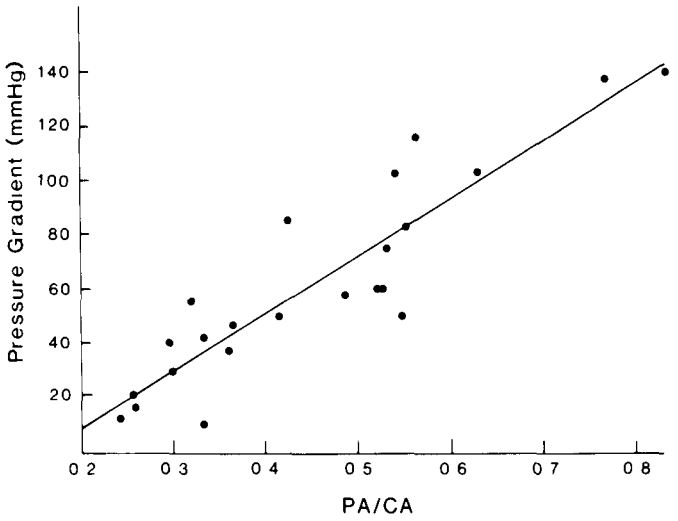
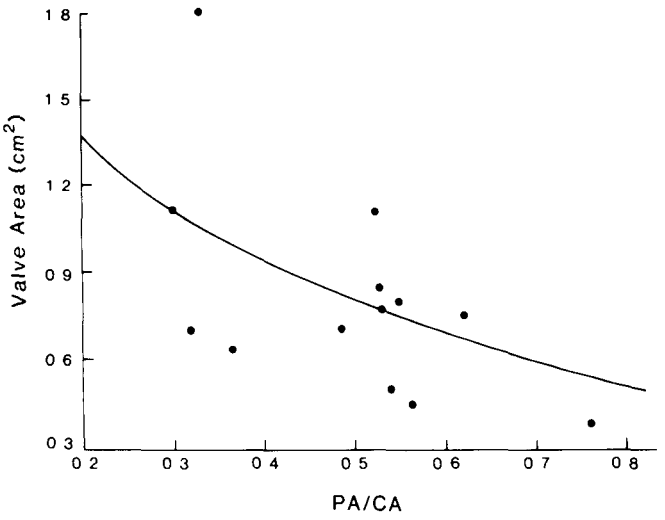


Figure 4. When predictive/control area (PA/CA) ratio derived from sound recordings in the aortic area was correlated with peak systolic pressure difference in all 23 patients, a high degree of correlation was found ($r = 0.90$, $p < 0.00001$, $f = 96$) as predicted by the equation: Pressure gradient = 214 (PA/CA) − 34.

had a significant gradient. Therefore, if the predictive/control area ratio of 0.4 or greater was considered predictive of severe stenosis, the sensitivity of the test was 93% and the specificity was 100%.

Predictive role of physical findings. The value of physical findings and noninvasive tests in predicting the severity of aortic stenosis varies with the prevalence of severe stenosis in the group of patients studied. In individual patients, physical findings predictive of severe aortic stenosis may be negated by a low cardiac output, concomitant aortic insufficiency and significant coronary artery disease. If the systolic blood pressure is low and the pulse pressure narrow, severe aortic stenosis is suggested (10), but these changes are found only in a minority of patients with severe aortic stenosis. A slowly increasing carotid pulse is highly suggestive, but less common in the elderly whose carotid vessels are less compliant because of arteriosclerosis (11). An S_4 gallop, which is highly predictive in a young person, is unreliable in the elderly patient because of frequently associated hypertensive and atherosclerotic coronary artery disease (12). A single second heart sound may be suggestive in a young person, but is found in a majority of normal persons over the age of 50 (13). Reversed splitting of S_2 is uncommon with aortic stenosis alone (14). A diminished or inaudible aortic closure sound is found in perhaps 20% of severe cases (7).

Figure 5. When predictive/control area (PA/CA) was correlated with the calculated valve orifice size in cm^2 in 13 patients, an inverse relation was found, but with poor predictability ($r = 0.60$, $p < 0.06$) as given by the equation: Valve Area = −0.6 ln (PA/CA) + 0.36.



Predictive role of noninvasive tests. Electrocardiographic evidence of left ventricular hypertrophy and strain is commonly associated with aortic stenosis (15), but does not quantitate severity and may mirror associated coronary artery disease or hypertensive heart disease, or both. The electrocardiogram may be normal in 10% or more instances of severe stenosis (16,17). Some findings are helpful in a negative sense. After age 40, failure to demonstrate valvular calcification at fluoroscopy suggests less than severe stenosis (18). Although increased aortic valve echoes are not specific for aortic stenosis in the older person, a normal aortic valve on M-mode echocardiogram excludes significant stenosis. More recently, two-dimensional echocardiography (19) has been applied to evaluate the severity of aortic stenosis with varying degrees of success, but the predictability is inadequate for making accurate clinical decisions. Combinations of tests further improve diagnostic specificity, but the sensitivity of the combination of diagnostic tests decreases. Bonner et al. (20) found three criteria useful in estimating severity: 1) left ventricular ejection time index greater than 0.42 second; 2) maximal arterial systolic dP/dt less than 500 Hg/s; and 3) Q to peak of murmur on the phonocardiogram greater than 0.19 second. Twenty-seven of 28 patients, many of whom were young, had all three criteria and had severe aortic stenosis. However, 27 of 36 patients with severe stenosis did not meet these criteria. For these reasons, most clinicians rely on cardiac catheterization to ensure an accurate diagnosis. No attempt was made to correlate the predictive accuracy of the predictive/control area (PA/CA) ratio with physical findings or other tests. Hence, coronary artery disease and aortic regurgitation may be expected to interfere with the predictability of physical findings and diagnostic tests. In this study, however, the predictive/control area ratio was highly predictive in this group of patients, although 9 (41%) of 22 patients had significant coronary artery disease and 14 (61%) of 23 had some degree of aortic regurgitation (Table 1).

Predictive algorithm for aortic stenosis: sources of error. Our predictive algorithm may have been biased by patient selection. It is possible that the algorithm may be less predictive in very elderly patients with severe calcific aortic stenosis and low cardiac output. Only 1 of 23 patients had an abnormally low cardiac index, but in this patient, predictive area/control area (PA/CA) ratio was predictive. The numerator of this predictive ratio reflects the higher frequency components of the aortic stenosis murmur and should be decreased by a low cardiac output. With low flow, the frequencies produced would be lower and the ratio should accurately predict a lower pressure gradient across the stenotic valve, but would underestimate the severity of the stenosis because the predictive/control area ratio is less predictive of the valvular cross-sectional area. If a low output state is suspected clinically, cardiac catheterization may be indicated. Calculation of a normal cardiac output by thermodilution, dye dilution or quantitative radionuclide ventriculography, however, could obviate invasive cardiac catheterization.

Musical systolic murmur. None of our patients had a musical murmur. A high frequency vibratory musical murmur in the aortic area, however, could overestimate the severity of aortic stenosis. The increased energy content of this high frequency, relatively pure tone murmur should increase the numerator of the predictive/control area ratio. Fortunately, musical murmurs in the aortic area are relatively uncommon and even if valvular stenosis was overestimated, cardiac catheterization would not be denied the symptomatic patient. Patients with a typical harsh murmur in the aortic area and a musical vibratory murmur at the left sternal border and apex (so-called Gallavardin dissociation) are unlikely to produce a misleading analysis because the recording was obtained in the aortic area.

Dilation of ascending aorta. Another potential source of error with this predictive algorithm could occur in patients with marked poststenotic dilation of the ascending aorta. In this setting, the higher frequency energy content of the murmur could be attenuated more than lower frequencies by the increased mass of blood contained in the large ascending aorta (21), resulting in a decrease in the predictive/control area (PA/CA) ratio.

Elderly patients and patients with aortic regurgitation. We have applied frequency analysis of the systolic murmur in more than 50 elderly people with presumed degenerative intimal thickening in the aorta, extending from the line of cusp attachment and without calcification of the aortic valve at image intensification fluoroscopy. The predictive/control area (PA/CA) ratio never exceeded 0.15 in this group of subjects. Similarly, 12 patients with pure aortic insufficiency documented at cardiac catheterization were studied and the predictive/control area ratio never exceeded 0.15. As shown, concomitant aortic insufficiency in 14 of 23 patients with aortic stenosis did not detract from the predictive accuracy of the algorithm. Other conditions associated with a systolic murmur, for example, pulmonary valve stenosis, ventricular septal defect and high output states, have not been studied.

Underestimation of valve area. The predictive/control area (PA/CA) ratio predicted the transvalvular pressure gradient better than it predicted valve area in the patients in our study with aortic stenosis. Failure to find a better statistical correlation with valve area may be explained in part by fewer data points for valve area and possible errors in valve area determination. Adequate data were available in only 13 of 23 patients. Cardiac output was measured by thermodilution, which is probably less accurate than other methods. Another contributing factor could be variable underestimation of valve area in some patients. The actual valve area is a fixed value that is unaffected by cardiac output. The predictive/control area ratio tracks the transvalvular pressure gradient, which varies with cardiac output as well as valve area. Cardiac output tends to decrease variably with increasing age and premedication. In addition, poststenotic dilation of the ascending aorta may affect the predictive/control area ratio in some patients, but would not affect valve area calculation. A better correlation of the predictive/control area ratio with aortic valve area may be found with further experience. The best fit for the inverse relation between predictive/control area ratio and valve area was exponential (Fig. 5).

Application to apical systolic murmurs. It was not unexpected to find that the predictive algorithm which related predictive/control area (PA/CA) to pressure gradient was applicable to murmur vibrations recorded in the second right intercostal space, parasternally, but not to murmurs recorded at the cardiac apex. There is evidence to suggest that higher frequencies are preferentially attenuated by the left ventricle and overlying lung parenchyma at the lower left sternal border and cardiac apex (22,23). This allows for selective transmission of the lower frequencies at the apex and accounts for the auscultatory illusion of a separate murmur at the apex in some patients. Higher frequencies generated at the stenotic aortic valve are least attenuated in the aortic listening area, an area closely related to the ascending aorta.

Clinical application. Although longitudinal studies have not been performed, it is expected that a significant change in the severity of aortic stenosis in a given patient will be associated with a significant change in the frequency spectrum and, therefore, in the predictive ratio, predictive/control area (PA/CA). Although this algorithm is highly correlated with the pressure gradient, it does not account for all of the variance of the data. Therefore, other factors that may influence the frequency spectrum must be evaluated, for example, skin-microphone coupling and poststenotic di-

lation. A larger cohort must be evaluated to optimize the algorithm and document its value as a noninvasive diagnostic test. We are currently evaluating a real-time analyzer that will simplify clinical application of this method.

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